

201-15267

Anh Nguyen

05/13/2004 06:51 AM

To: NCIC HPV@EPA

CC:

Subject: Fw: Comments on Reclaimed Substances Test Plan and Robust Summary: So
Naphthenates

dium

----- Forwarded by Anh Nguyen/DC/USEPA/US on 05/13/2004 06:51 AM -----



"Longfellow, David
(NIH/NCI)"
<longfeld@mail.nih.gov>

05/12/2004 05:33 PM

To: "hvp.chemrtk@epa.gov, chem.rtk@epa.gov, boswell.karen@epa.gov,
Grayt@api.org" <oppt.ncic@epa.gov>, >

cc:

Subject: Comments on Reclaimed Substances Test Plan and Robust Summary: So
Naphthenates

dium

CEB/DCB/NCI

Executive Plaza North - Suite 5000

6130 Executive Blvd MSC 7398

Bethesda MD 20892-7398

May 11, 2004

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ATTN: Chemical Right-to-Know HPV Challenge Program

RE: Comments on Reclaimed Substances Test Plan and Robust Summary

The National Cancer Institute Division of Cancer Biology (NCI/DCB) appreciates the opportunity to submit comments on the Robust Summary and Test Plan for Reclaimed Substances: Streams Containing Naphthenic Acids, Phenolics, Disulfides, Acids or Caustics. This information was submitted to the Environmental Protection Agency (EPA) by the American Petroleum Institute (API) Petroleum HPV Testing Group on December 15, 2003.

We would like to support the conclusions of the API Testing Group that additional studies are necessary to adequately characterize the hazard of naphthenic acids. This group has proposed that a 28-day combined, repeated-dose and reproductive/developmental toxicity screening test be conducted and that genetic toxicity be evaluated in that study. In addition, various testing for ecotoxicological endpoints is proposed.

One of the missions of the NCI Division of Cancer Biology is the dissemination of information on carcinogenic chemicals. To fulfill this mission, DCB screens the toxicological literature to identify chemicals that may require additional toxicological testing. Our program is supported and advised by the Chemical Selection Working Group (CSWG), a group of senior scientists and managers from various Federal Agencies, including other NCI programs, the EPA, the Food and Drug Administration, the Occupational Safety and Health Administration, the Consumer Product Safety Commission, the National Institute for Occupational Safety and Health, the National Institute for Environmental Health Sciences, and the National Library of Medicine.

NCI/DCB and the CSWG have a long-standing interest in naphthenates. In December 1983, the CSWG nominated cobalt naphthenate to the National Toxicology Program (NTP) for carcinogenicity testing. This testing was not conducted, mainly because of actions taken by the Interagency Testing Committee in 1983, recommending an extensive battery of testing for calcium naphthenate, cobalt naphthenate, and lead naphthenate. A test rule was not promulgated, in part, because of an ongoing skin painting study in mice which was later submitted to EPA by Shell Oil Company (EPA/OTS Doc. #0512234). In this study, 8 of 50 treated animals developed 12 epidermal and 1 dermal tumor vs 3 subcutaneous malignant tumors in control animals exposed to carrier oil.

The NCI/DCB has continued to have an interest in the naphthenates. In June 1989, the CSWG nominated calcium naphthenate, cobalt naphthenate, copper naphthenate, and sodium naphthenate to the NTP for chemical disposition studies. Concerns were expressed at a later date regarding the feasibility of conducting such studies on chemical mixtures such as the naphthenates and naphthenic acid, and testing was not conducted for this reason.

On July 1, 2003, NCI/DCB brought sodium naphthenate to the attention of the CSWG for possible nomination to the NTP for carcinogenicity testing. The intent was to evaluate a relatively water-soluble naphthenate with little toxicological information despite its high production volume and presence in the environment as a pollutant. The CSWG recommended that sodium naphthenate not be tested by the NTP because it is a close analogue of naphthenic acids, sponsored in the EPA HPV Challenge Program. The CSWG noted that testing sponsored by the manufacturers would be more appropriate since manufacturers would be in the best position to characterize a product most appropriate for testing.

NCI/DCB forwards this information to the EPA with a request that studies adequate to characterize the carcinogenic potential of sodium naphthenate/naphthenic acids be addressed in the test plan for reclaimed naphthenic acids.

Sincerely,

David G. Longfellow, PhD
Senior Coordinator for Chemical Carcinogenesis
Cancer Etiology Branch
Division of Cancer Biology

cc: Charles M. Auer, EPA

Enclosure

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SUMMARY OF DATA FOR CHEMICAL SELECTION

Sodium Naphthenate 61790-13-4

BASIS OF NOMINATION TO THE CSWG

Sodium naphthenate is brought to the attention of the Chemical Selection Working Group (CSWG) as a water-soluble naphthenate with little toxicological information despite its high production volume and presence in the environment as a pollutant.

Although sodium naphthenate was selected from a class study of plant growth regulators, it has other significant uses. A byproduct of the refining of jet fuels, diesel fuels, and kerosene, crude sodium naphthenate is recovered and sold to produce naphthenic acids, which are then converted to other high production volume metal soaps including calcium, copper, cobalt, and zinc naphthenates. Sodium naphthenate is specified in the production of copper naphthenate wood preservative. Sodium naphthenate and naphthenic acids are also environmental pollutants from the hydrocarbon industry and the extraction of oil from bitumen oil sands.

No adequate 2-year carcinogenicity study of sodium naphthenate, naphthenic acid, or the metal soaps was found in the available literature although limited information is available on calcium naphthenate. In *in vitro* studies, sodium naphthenate was not mutagenic in *Salmonella typhimurium* and did not induce chromosome aberrations in hamster ovary cells but it has been shown to cause sister chromatid exchanges.

Napthenate soaps have been considered for testing in the past. On December 15, 1983, the CSWG nominated cobalt naphthenate to the National Toxicology Program (NTP) with moderate to high priority for carcinogenicity testing based, in part, on the sarcomagenic activity of some cobalt compounds. In June 1989, the CSWG nominated calcium naphthenate, cobalt naphthenate, copper naphthenate, and sodium naphthenate for chemical disposition studies. Concerns were expressed at the Chemical Evaluation Committee review of this nomination about the feasibility of conducting chemical disposition studies on mixtures, and the recommendation

for testing the chemical disposition of a single naphthenic acid was made. Some problems with the supply of a naphthenic acid appropriate for testing appears to have occurred, and the testing was never performed (Easton, 2003).

The Twelfth Report of the Interagency Testing Committee (ITC) recommended an extensive battery of testing for calcium naphthenate, cobalt naphthenate, and lead naphthenate, including carcinogenicity, mutagenicity, teratogenicity, toxicokinetics, and reproductive effects (EPA, 1983).

In its response to the ITC on May 21, 1984, The US Environmental Protection Agency (EPA) indicated that data being developed in ongoing testing in conjunction with available health effect information should provide sufficient information to reasonably determine or predict the risks of the health effects recommended for testing by the ITC for each of the three metal naphthenates. For calcium naphthenate, EPA noted two on-going health effects studies sponsored by Shell International Chemical Company, a skin painting study in mice and a reproductive effects study in rabbits. EPA noted that cobalt naphthenate had been nominated for testing by the NTP. Dermal absorption studies were also being designed by the Chemical Manufacturers Association to determine whether cobalt is absorbed into the blood of rats after repeated dermal applications of a paint product (EPA, 1984).

INPUT FROM GOVERNMENT/INDUSTRY

Dr. William Easton, National Institute of Environmental Health Sciences, provided information on the status of naphthenates within the NTP. Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC), provided information on EPA's decision on metal naphthenates.

SELECTION STATUS:

Rejected

Action by CSWG:

July 1, 2003

Comments:

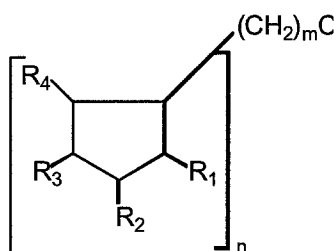
This substance was rejected for testing by the NTP because it and/or a close analogue is a sponsored chemical in the EPA HPV Challenge Program. The group felt that the testing of this substance for carcinogenicity is appropriate but should be performed by the manufacturers who are in a better position to identify the appropriate mixture for testing.

CHEMICAL IDENTIFICATION

CAS Registry No.: 61790-13-4

Synonyms: Naphthenic acids, sodium salts; naphthenic acid, sodium salt; sodium naphthenate solution, NK 270; Valirex® Sodium (ChemFinder.com, 2003; ChemID, 2003; Van Loocke, 2003)

Structure, Molecular Formula, and Molecular Weight:



Structural Class: Alkyl-substituted cycloaliphatic carboxylic acids

Chemical and Physical Properties:

Description: White paste, yellow crystalline solid, consistency of grease (Fisher Scientific, 2000; Lewis, 2002)

Density: 1.059 g/cm³ at 20 °C (NTP, 2001)

Flash Point: >93.3 °C (NTP, 2001)

Melting Point: 125-146 °C (BIBRA Toxicity Profile, 1999)

Solubility: Soluble in water, acetone, and 95% ethanol (BIBRA Toxicity Profile, 1999; NTP, 2001)

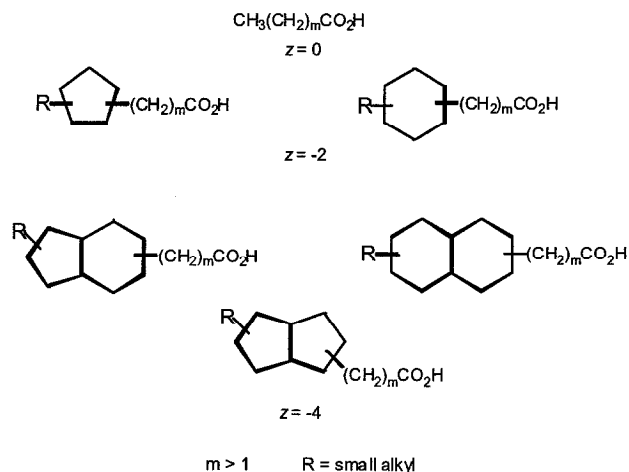
Reactivity: Emulsifying and foam-producing properties; low hydrolytic dissociation; incompatible with strong oxidizing agents; combustible (Fisher Scientific, 2000; Lewis, 2002; NTP, 2001)

Technical Products and Impurities:

Sodium naphthenate (practical grade) is available from Fisher Scientific (Fisher Scientific, 2003).

Sodium naphthenate is the sodium salt of naphthenic acids. Naphthenic acids [CAS No. 1338-24-5] are a complex mixture of alkyl-substituted acyclic and cycloaliphatic carboxylic acids, predominantly monocarboxylic acids (Holowenko *et al.*, 2002; Sisco *et al.*, 1981). The composition of naphthenic acids has been shown to vary in petroleum samples from different sources of oils and their source rocks. Due to the variety of acids present in naphthenic acid distillates, the molecular weight of naphthenic acids also changes. One report specified an average molecular weight of 200-300 (BIBRA Toxicity Profile, 1999).

Naphthenic acids have a general formula of $C_nH_{2n+z}O_2$, where n indicates the carbon number and z specifies a homologous series (Holowenko *et al.*, 2001 & 2002). The main distinguishing structural characteristic of naphthenic acids is a hydrocarbon chain consisting of single or fused cyclopentane rings alkylated in various positions with short aliphatic groups. Other acids such as aliphatic and dicarboxylic, and those containing the cyclohexane ring, are also present in moderate quantities (Sisco *et al.*, 1981). Examples of naphthenic acid structures are shown below (Holowenko *et al.*, 2001).



The composition of naphthenic acids in a commercial sample of sodium naphthenate,

manufactured by The Eastman Kodak Company, is shown in Tables 1 and 2. Compounds with carbon numbers (n) of 13-18 comprised 77% of the acids in this commercial sample. The most abundant acids were distributed evenly in the $z = 0$, -2 , and -4 families, accounting for 81% of the total acids (Holowenko *et al.*, 2001).

Table 1. Distribution of Carbon Numbers (n) in a Commercial Source of Sodium Naphthenate

Carbon Number (n)	Percentage of the Total Naphthenic Acids
7	2 ± 1
8	1 ± 1
9	1 ± 0
10	1 ± 1
11	2 ± 2
12	4 ± 1
13	7 ± 1
14	11 ± 6
15	17 ± 5
16	19 ± 8
17	15 ± 2
18	8 ± 2
19	5 ± 1
20	3 ± 0
21	1 ± 1
22	0

Source: Holowenko *et al.*, 2001

Table 2. Distribution of α Families in a Commercial Source of Sodium Naphthenate

α Family	No. of Rings	Percentage of the Total Naphthenic Acids
0	0	26 ± 5
-2	1	28 ± 4
-4	2	27 ± 1
-6	3	12 ± 2
-8	4	4 ± 1
-10	5	3 ± 1
-12	6	1 ± 0

Source: Holowenko *et al.*, 2001

Naphthenic acids are viscous liquids with a characteristic odor resulting from the phenols and sulfur compounds which are extracted along with the acids when they are recovered as by-products from the refining of straight-run petroleum distillates. The properties of crude naphthenic acids and their impurities can vary widely depending on their source and the refining methods. The average molecular weight is higher for acids extracted from higher boiling fractions. The content of the odorous impurities is reduced and the color improved for distilled grades of naphthenic acids compared with the corresponding crudes (Sisco *et al.*, 1981).

EXPOSURE INFORMATION

Producers:

According to Chemical Sources International (2003), there are 7 US suppliers of sodium naphthenate.

Production:

Manufacturing Processes: Sodium naphthenate is a byproduct of the refining of petroleum products. The hydrocarbon industry uses caustic solutions to extract or treat acidic impurities such as hydrogen sulfide, mercaptans, and organic acids in hydrocarbon streams. Refinery gas, liquefied petroleum gases, and light naphthas are almost all treated with caustics. Sulfur compounds in heavy fractions such as heavy naphtha, jet fuel, and diesel are not caustic extractable. These fractions undergo caustic sweetening which produces organic byproducts, including sodium naphthenate. Naphthenic caustic solutions can be sold to outside processors who neutralize the solutions and recover naphthenic acids for naphthenate metal salt producers. Typical refinery naphthenic caustic streams contain 2-15% by weight of naphthenic acids and 1-4% by weight of sodium hydroxide (Suarez, 1999; US Trade and Development Agency, 1999; Washington State, 2002).

Production/Import Levels:

Sodium naphthenate is listed in EPA's Toxic Substances Control Act (TSCA) Inventory (ChemID, 2003).

Sodium naphthenate is a high production volume (HPV) chemical with annual production exceeding 1 million pounds in the US. It is sponsored with full commitment by the American Petroleum Institute in the HPV Challenge Program (EPA, 2003).

Use Pattern:

Sodium naphthenate has the following uses:

- detergent, emulsifier, disinfectant (Brient *et al.*, 1995; Lewis, 2002)
- chemical intermediate used to produce naphthenic metal soaps (Brient *et al.*,

1999; Dynamac Corporation, 1982; Lewis, 2002)

- component of insecticidal agricultural sprays (A.G.S. Chemical Products Ltd., 2003)
- component in lubricating additives (walshcarlines.com, 2003)
- recovery of rare-earth metals using ore flotation (Brient *et al.*, 1995)
- leather tanning (Brient *et al.*, 1995)

Sodium naphthenate, with copper sulfate can be used to produce copper naphthenate wood preservative under the American Wood Preservers' Association Standard P-8 for copper naphthenate (Brient *et al.*, 1999).

Although no indication that naphthenic caustic solutions are imported or exported to produce naphthenic acids was found, naphthenic acids are also HPV chemicals (EPA, 2003). The Port Import/Export Reporting Service (PIERS) reported naphthenic acids exports with a cargo weight of 565,868 pounds over the 17-month period from November 2001 to March 2003 (Dialog Information Service, 2003).

A total of 93 patents using sodium naphthenate were on file with the US Patent and Trademark Office since 1976 as of May 2003 (US Patents and Trademark Office, 2003).

Human Exposure:

Occupational Exposure: Exposure to naphthenic caustic solutions can occur in the hydrocarbon processing industry from leaks or spills during processing, during transfer as chemical feedstocks to outside chemical processors, and during equipment maintenance. Chemical processors can be exposed to naphthenic caustic solutions from leaks and spills during the manufacture of naphthenic acids.

Naphthenic acids are normal constituents present in Athabasca oil sands mined and extracted in Canada, an industry that is projected to produce as much as 400 million barrels of oil annually. Most of the present production is based on the Clark caustic hot water

extraction process that produces naphthenates as a byproduct (Holowenko *et al.*, 2002; Horváth-Szabó *et al.*, 2001). Thus, workers in this industry are also potentially exposed to crude sodium naphthenate solutions.

Environmental Exposure: Environmental pollution may occur when naphthenic caustic solutions are produced in poorly designed and mismanaged facilities, and during transferring as chemical feedstock to chemical processors outside of refineries (Suarez, 1999).

Naphthenic acids are an important component of the waste generated during processing of petroleum from oil sands and oil deposits (AccessScience, 2002; Brient *et al.*, 1995; Rogers *et al.*, 2002a).

In Canada, Athabasca oil sands companies contain process-affected waters and fluid tailings on site, primarily in large settling ponds. It is estimated that 1 billion cubic meters of tailings pond water will have accumulated by 2025 as the result of mining Athabasca oil sands. In fresh tailings waters, naphthenic acids concentrations may exceed 100 mg/l (Holowenko *et al.*, 2002; Leung *et al.*, 2003; Rogers *et al.*, 2002a).

Environmental Occurrence:

Natural Sources: Naphthenic acids are natural constituents of petroleum that evolve through the oxidation of naphthenes (cycloalkanes). These saturated mono- and polycyclic carboxylic acids can account for as much as four percent of raw petroleum by weight (AccessScience, 2002; Rogers *et al.*, 2002a).

Naphthenic acids are found at concentrations up to 1-2 mg/l in natural surface waters of the Athabasca oil sands region due to erosion of exposed oil sands formations (Leung *et al.*, 2003).

Water Pollution: Separation of bitumen from other components of Athabasca oil sands by

the Clark caustic hot-water extraction method dissolves naphthenic acids which are concentrated in tailings water. These tailings, amassed in large holding ponds in the immediate area, are acutely toxic to aquatic organisms and represent a long-term source of naphthenic acid exposure to indigenous wildlife (Holowenko *et al.*, 2002; Leung *et al.*, 2003; Rogers *et al.*, 2002a).

In traditional refining operations that do not sell their naphthenic caustics, dilute caustic prewash systems interact with naturally occurring naphthenic acids to form sodium naphthenates that add to the loading of the wastewater treatment plant. Traditional waxy crude oils generate only modest quantities of sodium naphthenate. Crude oil slates are more acidic, causing the amount of sodium naphthenate to increase greatly. This overload tends to disrupt spent caustic tank operations and wastewater treatment operations (Washington State, 2002).

A 2002 report on alternative processes to prevent water pollution in petroleum refineries described the elimination of caustic washing as not economically justified. The report concluded that caustic washing is likely to remain the technology of choice to treat acidic impurities in crude oils (Washington State, 2002).

Biodegradation: Sodium naphthenate was biodegraded by 50 percent within 24 days (Metal Carboxylates Coalition, 2002a).

Naphthenic acids can undergo microbial biodegradation under aerobic conditions. In oil tailings, compounds with methyl substitution on the cycloalkane ring were more resistant to biodegradation while microbial activity against certain carboxylated cycloalkanes was nitrogen and phosphorus limited (Herman *et al.*, 1993; Leung *et al.*, 2003).

Environmental Toxicity: Several reports have identified naphthenic acids as the principal acute toxicant in oil sands process-affected waters. Water associated with fresh tailings was acutely toxic to aquatic organisms, including *Selenastrum capricornutum*, *Daphnia magna*,

Hyaella azteca, *Oncorhynchus mykiss*, and *Photobacterium phosphoreum*. Biodegradation of naphthenic acids in water decreased or eliminated toxicity in *Photobacterium phosphoreum* (Herman *et al.*, 1994; Holowenko *et al.*, 2002; Leung *et al.*, 2003; Rogers *et al.*, 2002a).

The results of several acute and subchronic toxicity studies of sodium naphthenate in aquatic and terrestrial species are summarized in Table 3.

Table 3. Ecotoxicity Values for Sodium Naphthenate

Organism	Study Time	Toxicity Endpoint	Toxic Dose (mg/l)
<i>Rutulis frisii</i> kutum (kutum)	96 hr	LC ₅₀	50
		LC ₅₀	2
<i>Acipenser gueldenstaedi</i> (sturgeon)	96 hr	LC ₅₀	50
	60 days	LC ₅₀	11
<i>Rutulis rutulis</i> caspicus (roach)	96 hr	LC ₅₀	75
	60 days	LC ₅₀	14
<i>Nitzschia linearis</i> (diatom)	96 hr	EC ₅₀	43

Source: Leung *et al.*, 2003; Rogers *et al.*, 2002a

Regulatory Status:

No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace allowable levels of sodium naphthenate. Sodium naphthenate was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) are made.

Naphthenic caustic solutions are not subject to regulation under the Emergency Planning

and Community Right-to-Know Act (EPCRA) and they are not classified under the Resource Conservation and Recovery Act (RCRA) as waste when they are processed for beneficial reuse (Suarez, 1999).

Naphthenic acids are listed in the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) as a hazardous waste. The reportable quantity (RQ) of naphthenic acids is 100 lb as specified in 40 CFR 302.4. Naphthenic acids are also designated as a hazardous substance under the Clean Water Act (HSDB, 2003).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data:

No epidemiological studies or case reports investigating the specific association of exposure to sodium naphthenate and cancer risk in humans were identified in the available literature.

Animal Data:

Acute Studies: The oral LD₅₀ for sodium naphthenate was reported to be 3.55 g/kg bw in male mice, producing central nervous system depression, convulsions, and respiratory arrest leading to death (Rogers *et al.*, 2002a).

Moderate irritation after skin or eye contact to naphthenic acids was observed in rabbits (BIBRA Toxicity Profile, 1999).

Wistar rats were gavaged once at 3, 30, or 300 mg/kg bw (females) or 300 mg/kg bw (males) with naphthenic acids extracted from oil sands tailings ponds. Fourteen days later, the high-dose group of both sexes had a significant incidence of pericholangitis, high dose males also had brain hemorrhage, and high dose females had cardiac periarteriolar necrosis and fibrosis (Rogers *et al.*, 2002a).

Subchronic Studies: No information on the effects of subchronic exposure to sodium naphthenate was identified in the available literature.

Significant increases in the relative weights of the liver, kidney, and brain were reported in female Wistar rats administered naphthenic acids extracted from oil sands tailings pond water by gavage (0, 0.6, 6, and 60 mg/kg/day), 5 days/week for 90 days. Liver glycogen accumulation was the only dose-related histological change observed in these animals. High-dose rats also had higher blood amylase and lower plasma cholesterol levels than controls (Rogers *et al.*, 2002a).

Chronic/Carcinogenicity Studies: No 2-year carcinogenicity studies of sodium naphthenate

or naphthenic acids were identified in the available literature.

Short-Term Tests:

Sodium naphthenate was not mutagenic when tested in *Salmonella typhimurium* with or without S-9. Sodium naphthenate did not induce chromosome aberrations in hamster ovary cells but it was positive for sister chromatid exchanges. These studies were carried out with and without S-9 (BIBRA Toxicity Profile, 1999; NTP, 2003).

Sodium naphthenate protected against chromosome damage induced by γ -irradiation in the onion (*Allium fistulosum*) (Gurvich & Shcherbakov, 1969).

Naphthenic acids were not mutagenic when tested in *Salmonella typhimurium* (Brient *et al.*, 1995).

Other Biological Effects:

Reproductive Toxicity: No information on the developmental or reproductive effects of sodium naphthenate was identified in the available literature.

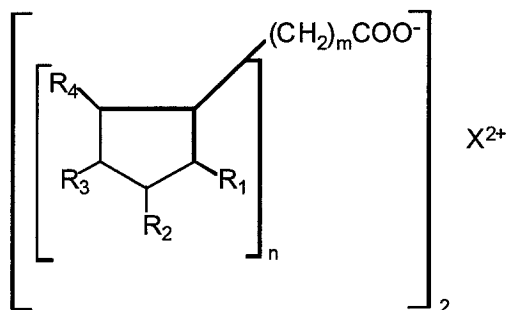
Oral administration of naphthenic acids at 6 or 60 mg/kg/day to female Wistar rats during pre-breeding, breeding, and gestation caused infertility in the high-dose group of animals. Fetal malformations were not observed in any offspring (Rogers *et al.*, 2002b).

Structure-Activity Relationships:

Four naphthenate metal soaps (calcium naphthenate [111-84-2], cobalt naphthenate [629-50-5], copper naphthenate [1338-02-9], and zinc naphthenate [12001-85-3]) were screened for information on genotoxicity and carcinogenicity.

Unlike sodium and potassium naphthenate, which are water-soluble, calcium, cobalt, copper, and zinc naphthenates are poorly soluble in water. These compounds are soluble in oils and nonpolar organic solvents (Dynamac Corporation, 1982).

The general structural formula for the selected compounds is shown below.



R₁-R₄ are hydrogen atoms and alkyl (usually methyl)
n = 1-5 fused rings (usually 1-2)
m = 0-4 (often 1)
X = Ca, Co, Cu, Zn

No carcinogenicity bioassays conducted to modern regulatory standards were available for any of the naphthenates. The information identified in the available literature for these naphthenates is summarized in Table 4.

Table 4. Data on Compounds Structurally Related to Sodium Naphthenate

Name/CAS No.	Results of Studies of Carcinogenic and Genetic Toxicity
Calcium Naphthenate 61789-36-4	<p>L5178Y (TK+/-) mouse lymphoma cells w/o S-9: Positive (CCRIS, 2003)</p> <p><i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, & TA1538 w/wo S-9: Negative (Shell Oil Co., 1983a)</p> <p><i>E. coli</i> WP2 and WP2 <i>uvrA</i> w/wo S-9: Negative (Shell Oil Co., 1983a)</p> <p><i>S. cerevisiae</i> w/wo S-9: Negative (Shell Oil Co., 1983a)</p> <p>Chromosome aberrations in rat liver cell cultures w/wo S-9: Negative (Shell Oil Co., 1983a)</p> <p>STCF mice (50 females); epidermal dose of 0.05 ml of SAP 011 (calcium naphthenate) in mineral oil, 2/wk for 104-106 wk; positive: 12 epidermal and 1 dermal tumor at treated sites in 8 mice (16%) (4 malignant and 9 benign tumors); 3 animals exposed to carrier oil developed subcutaneous malignant tumors; histopathology was performed only in skin tissue (Shell Oil Co., 1986)</p>

<p>Cobalt Naphthenate 61789-51-3</p>	<p><i>S. typhimurium</i> TA100 and TA1537 w/wo rat or hamster liver S-9: Negative (CCRIS, 2003)</p> <p><i>S. typhimurium</i> TA98 and TA1538 w/wo hamster liver S-9: Negative (CCRIS, 2003)</p> <p><i>S. typhimurium</i> TA98 and TA1538 w/rat liver S-9: Positive (CCRIS, 2003)</p> <p>Mice (30/group); intramuscular dose; 0.02 ml (as 7% metallic Co) for 14 mo; positive: 8 tumors at injection sites in 8 animals (4 granular rhabdomyomas, 4 rhabdomyosarcomas) (Chemical Manufacturers Association, 1983; Dynamac Corporation, 1982)</p> <p>Rabbits (12 males); several routes; doses of 0.4-0.8 ml (as 1% metallic Co) 2-4/wk for 2-6 mo; positive: 9 rabbits developed tumors; intravenous and intramuscular routes induced tumors at injection sites; intrahepatic or pleural injections produced hemangioendothelioma and pleural mesothelioma, respectively (Chemical Manufacturers Association, 1983; Dynamac Corporation, 1982)</p> <p>Rabbits (10), intravenous doses; positive: 5 rabbits developed tumors after 1-2 yrs (Dynamac Corporation, 1982)</p>
<p>Copper Naphthenate 1338-02-9</p>	<p><i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, and TA1538 w/wo S-9: Negative (CCRIS, 2003; Metal Carboxylates Coalition, 2002b)</p> <p>L5178Y (TK+/-) mouse lymphoma cells w/wo S-9: Positive (California Environmental Protection Agency, 2000; CCRIS, 2003)</p> <p>L5178Y (TK+/-) mouse lymphoma cells wo/S-9: Negative (Metal Carboxylates Coalition, 2002b)</p> <p>Chromosome aberrations in CHO cells w/wo S-9: Negative (California Environmental Protection Agency, 2000; Metal Carboxylates Coalition, 2002b)</p>
<p>Zinc Naphthenate 12001-85-3</p>	<p>L5178Y (TK+/-) mouse lymphoma cells w/wo S-9: Positive (California Environmental Protection Agency, 2000; CCRIS, 2003; Metal Carboxylates Coalition, 2002b)</p> <p>Chromosomal aberrations in CHO cells w/wo S-9: Positive (California Environmental Protection Agency, 2000; Metal Carboxylates Coalition, 2002b)</p> <p>UDS in rat primary hepatocyte cultures: Negative (California Environmental Protection Agency, 2000; Metal Carboxylates Coalition, 2002b)</p>

Abbreviations: CHO = Chinese hamster ovary; *E. coli*=*Escherichia coli*; *S. cerevisiae*=*Saccharomyces cerevisiae*; UDS = unscheduled DNA synthesis; w=with; wo=without

References

AccessScience (2002) *Oil Sand*. The McGraw-Hill Companies. [<http://www.metrostate.edu/>]. Searched May 2, 2003

A.G.S. Chemicals and Products Ltd. (2003) *Preservatives (Fungicides and Insecticides)*. A.G.S. Chemicals Specialist suppliers of Naphthenic Acid. [<http://www.amtrade.co.uk/app04.htm>]. Searched January 23, 2003

BIBRA Toxicity Profile (1999) *Naphthenic Acid and its Sodium, Calcium and Manganese Salts*, 2nd ed., Carshalton, Surrey, UK, BIBRA International Ltd.

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